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Review

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The importance of treating dental caries in the prevention of medication related osteonecrosis of the jaw

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ABSTRACT

Antiresorptive agents such as bisphosphonates, denosumab and zoledronic acid may induce medication-related osteonecrosis of the jaw (MRONJ). MRONJ is a rare but serious side effect caused by medications such as bisphosphonate and denosumab, which are used as antiresorptive medications in malignancies related to bone metastases and bone metabolism diseases. Since the major predisposing factor of this side effect may be tooth extraction, our aim in this review is to show that preventing the emergence of pathology in dental hard tissues and treating it when it occurs with a preventive and therapeutic strategy, providing adequate oral hygiene, and motivating the patient for its continuity could reduce the risk of the occurrence of MRONJ by reducing the need for oral surgery in terms of restorative dental treatment.

Keywords: MRONJ, bisphosphonates, dental caries treatment, tooth extraction

INTRODUCTION

Antiresorptive agents such as bisphosphonates, denosumab and zoledronic acid may induce medication-related osteonecrosis of the jaw (MRONJ). MRONJ can occur as a side effect of high doses of agents that modify bone metabolism, such as zoledronic acid and denosumab, in patients with multiple myeloma and in cancer patients with bone metastases. Although MRONJ can occur in both jaw bones (4.5%) in the maxillofacial region, it has been observed that it is a pathological process that can be seen in the mandible (75%) rather than the maxilla (25%).[1-3] It has been reported that MRONJ, which is rarely seen, is characterized by progressive bone destruction, usually with exposed necrotic bone in the oral cavity or skin, accompanied by swelling, pain, and a fistula lasting for 8 weeks or longer.[4] Studies have suggested that invasive procedures such as tooth extraction may be a major risk factor for the onset of MRONJ, and it has been suggested that tooth extraction should be avoided in the patient group using drugs that cause MRONJ.[5-7]

In studies conducted among patients with MRONJ, it was reported that tooth extraction played a role as a predisposing factor in the occurrence of osteonecrosis, with rates ranging from 62% to 82%.[2,3,8] Although the reasons for tooth extraction include dental caries, periodontal problems, endodontic reasons, eruption failures, and part of prosthetic planning, the main reason is dental caries.[9-16] Our aim in this review is to show that preventing the occurrence of dental pathology and treating it when it occurs by using preventive and therapeutic strategies in terms of restorative and dental treatment, providing adequate oral hygiene, and motivating the patient to maintain oral hygiene can reduce the risk of MRONJ by reducing the need for oral surgery.

HISTORY

Osteonecrosis developing in the jaws due to bisphosphonates was first described by Marx and Stern in 2002 as a condition in which "bone is exposed, which does not heal with debridement and worsens and expands in area," which is the classical approach to surgery.[19] And this condition was reported to those concerned in 2003 in the "Journal of Oral and Maxillofacial Surgery" with a medical alert in which 36 cases of Pamidronate or Zoledronate-related cases were described.[20] Later, a similar condition was reported by Ruggiero et al.[21] in 2004, and by 2009, this pathologic event was reported as bisphosphonate-related osteonecrosis of the jaw bones (BRONJ) by the American Society for Maxillofacial Surgery.In 2014, upon the realization that not only bisphosphonates but also antiresorptive and antiangiogenic drugs can cause osteonecrosis, the new nomenclature was updated as drug-associated osteonecrosis

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of the jaw bones (MRONJ), according to the current status report published by the American Association for Maxillofacial and Facial Surgery.[1] MRONJ is the terminology we have used throughout this review.

MEDICINES CAUSING MRONJ

The first group of drugs associated with MRONJ were the bisphosphonates pamidronate (Aredia®) and zoledronic acid (Zometa®). By blocking osteoclasts, these drugs were used to treat people whose cancer had spread to their bones. Later, new cases of MRONJ were reported after the discovery of denosumab (XGeva®), a humanized monoclonal antibody that works in a similar way on osteoclasts. Denosumab blocks RANK-RANKL binding and inhibits osteoclast function by inhibiting osteoclast inhibition. Administered subcutaneously every 6 months, it has been reported to provide a significant reduction in the risk of vertebral and hip fractures in osteoporosis patients.[22] It has also been reported that denosumab reduces bone metastases and the metastatic spread of solid tumors when administered monthly.[23-25] Romosozumab, another monoclonal antibody used subcutaneously, prevents fractures by increasing bone formation and decreasing resorption in osteoporotic women.[26]

Other drug groups, including antiangiogenic drugs, targeted therapy, and biological immunomodulators, have also been associated with MRONJ. It has been suggested that cancer patients treated with bisphosphonates and antiangiogenic drugs in combination may have an increased risk of MRONJ.[27]

Mechanism of Action of Medicines That Cause MRONJ

Drugs causing MRONJ to accumulate in the bone matrix depending on the repeated dose amount, duration, and route of administration. Since bisphosphonates are resistant to hydrolytic degradation, their half-life in the bone matrix is longer than 11 years.[28] They are stored in the bone matrix by binding to hydroxyapatites and then released and absorbed by osteoclasts.[29] This group of drugs has a toxic effect on osteoclasts, suppressing their functions and reducing their population by causing apoptosis.[30] As a result, there is a decrease in bone formation and destruction.[31] This is a human monoclonal antibody called denosumab. It works against the receptor activator of the Nuclear Factor Kappa B ligand. It inhibits RANK-RANKL binding and prevents its function by providing osteoclast inhibition.[26]

Why are MRONJ-Related Medicines Used?

Bone metastases may cause several of skeletal-related problems, including clinically defined pathologic fractures, spinal cord compression, hypercalcemia, and pain severe enough to require radiotherapy or surgery.[32] Bisphosphonates are antiresorptive drugs and are used to stabilize osteolysis, which allows the metastatic spread of malignancies associated with bone metastases such as breast cancer, prostate cancer, lung cancer, and multiple myeloma, and to reduce hypercalcemia associated with malignancies.[2]

Multiple myeloma is a pathology of plasma cells and is a rare but serious disease that leads to the uncontrolled production of these cells and their destruction by spreading to the surrounding bone tissue. It accounts for about 1% of all tumors and typically occurs in older people. These tumors can cause bones to become weaker and more susceptible to fracture. Patients affected by multiple myeloma have been found to have a higher risk of developing MRONJ due to the bisphosphonate used for treatment compared to patients treated with bisphosphonates for other diseases (for example, patients with bone metastases from advanced breast or prostate cancer).[33]

Metastatic Breast Cancer; Bone is the most common site of metastasis in patients with breast cancer. Approximately 65-75% of advanced-stage patients may develop bone metastasis. Bone-modifying bisphosphonates play an important role in the treatment of women with early and advanced metastatic breast cancer. When bisphosphonates are added to standard treatment for women with metastatic breast cancer, the risk of problems with their bones goes down by 15%. There are also delays in the start of these problems and less pain.[32] Prostate cancer, this type of cancer also metastasizes, especially to bone, with 90% of patients in the metastatic stage having bone metastases.[34] In addition, the MRONJ-related drug group is also used in the treatment of osteoporosis, osteopenia, the prevention of osteoporosis-related fractures, Paget's disease, and osteogenesis imperfecta.[35-37]

MRONJ DIAGNOSTIC CRITERIA

MRONJ is a side effect of antiresorptive drugs characterized by an exposed necrotic jawbone in the jaws in patients who have used or are using one or more of the drugs associated with the complications. The diagnosis of MRONJ is based on clinical findings rather than histopathology and radiographic data. Clinical findings and anamnesis are the most important tools for differential diagnosis. The following three criteria should be considered when diagnosing MRONJ:[38]

1. There is no history of radiotherapy to the jaws and no history of metastatic disease in the jaws.
2. The person has been or is currently being treated with bone-modifying drugs (such as bisphosphonates, denosumab, or antiangiogenics).
3. Exposed necrotic bone detected intraoral or extraoral in the maxilla or mandible for more than 8 weeks.

WHY DOES MRONJ OCCUR IN THE JAWS?

Many possible factors, such as trauma, surgical extraction, inadequate wound healing, changes in oral bacterial biofilm profile, and impaired immune response specific to the oral cavity, have been considered possible reasons for the occurrence of MRONJ, mostly in the jaws.[39] However, despite many years of research, it is still not fully understood why MRONJ occurs mostly in the jaws.[40] Nevertheless, several hypotheses have been proposed in the literature. First, it has been suggested that anti-resorptive drugs, which slow down bone metabolism, can cause necrosis. These drugs can reach higher concentrations in the jaw bones because they are used up and replaced so quickly. Secondly, anti-resorptives such as bisphosphonates administered intravenously in clinically high doses impair oral mucosal healing processes by inhibiting the proliferation of oral mucosal keratinocytes, while the jaw bones, covered by a thin mucous membrane, are particularly prone to injury during dental prosthetics or

dental treatments, In addition, it has been suggested that the antiangiogenic properties of anti-resorptives impair healing, allowing microorganisms to penetrate into the underlying bone and secondary infection to occur, and that the weakened immune response of patients undergoing chemotherapy also promotes infection.[41]

RISK FACTORS OF MRONJ

MRONJ has emerged as a complication of antiresorptive drugs, and its etiology is multifactorial.[1] Risk factors shorten the time to the onset of MRONJ and increase the rate and severity of development. Early reports on MRONJ indicated the pathologic condition as a specific side effect of high-dose, intravenous, and nitrogen-containing formulations of bisphosphonates. The risk of MRONJ in patients taking bisphosphonates was found to be significantly higher, especially in patients taking intravenous bisphosphonates such as Zoledronate. This difference has been attributed to the higher efficacy, bioavailability, and longer accumulation in bone compared to oral bisphosphonates.[42]

Invasive procedures

It has been reported that dentoalveolar operations may be the most common predisposing factor and that tooth extraction increases the susceptibility to MRONJ among patients with MRONJ at rates ranging from 62% to 82%.[2,3,8] Since invasive procedures such as tooth extraction may be a major risk factor for the onset of MRONJ, it has been shown that tooth extraction should be avoided in these patients.[5-7] However, some clinical data have shown that the risk of MRONJ goes down if the infected tooth is removed, even if antiresorptive therapy is not stopped.[43] Nevertheless, several studies have found that the risk of MRONJ occurrence is very high, with dental trauma associated with local infection, abscess, and poor oral hygiene.[44,45]

Periodontal and dentoalveolar infections

Otto et al.[33] stated that local infections rather than tooth extraction may be an important risk factor in the development of MRONJ, and dentoalveolar surgery should not be avoided in cases that cannot be treated with conservative measures.In many studies, mice with experimentally induced rheumatoid arthritis showed more severe MRONJ, with large areas of exposed bone and severe necrosis.[46]

Poor oral hygiene has been frequently emphasized as a fundamental factor in the prevention of infections in drug-treated patients at risk of osteonecrosis. Poor oral hygiene conditions may lead to various opportunistic infections. Inadequate oral hygiene has been listed among the factors affecting the occurrence of MRONJ.[47]

Trauma, excess occlusal force due to incompatible prosthesis use, and secondary trauma. Studies have revealed that the risk of jaw necrosis in naive patients using antiresorptive drugs increases due to factors such as bacterial, viral, and fungal infections, trauma, smoking, steroid use, a weakened immune system, autoimmune diseases, diabetes, and chemotherapy.[48]

CAN MRONJ DEVELOP SPONTANEOUSLY?

In a small percentage of patients on antiresorptive medication, osteonecrosis of the jaw occurs spontaneously (spontaneous). "Spontaneous" cases of MRONJ have been associated with specific anatomical sites, including the torus, exostoses, and mylohyoid ridges. The exostoses, torus, and mylohyoid ridges are particularly at risk of ulceration due to trauma because of their physical prominence, reduced circulatory ability, and thickness of overlying tissue. If "spontaneous" MRONJ is associated with anatomical sites at risk of oral trauma, perhaps the term "spontaneous" may be a misleading nomenclature, and there may in fact be a low level of trauma to the delicate oral mucosa. Given this circumstance, it might be necessary to explain to patients during patient education that oral food intake trauma can also predispose to the development of MRONJ.[49]

MRONJ STAGING SYSTEM

Stage 0

Patients without clinical evidence of necrotic bone but with vague symptoms or clinical and radiographic findings.

Stage 1

Presence of an exposed and necrotic bone or fistula in asymptomatic patients with no signs of infection/inflammation.

Stage 2

Patients with exposed and necrotic bone or bone-related fistula and signs of infection/inflammation.

Stage 3

Exposed and necrotic bone or bone-associated fistula, showing signs of infection, may include one or more of the following:

Exposed necrotic bone extending beyond the alveolar bone region (e.g., lower border and ramus of the mandible, maxillary sinus, and zygoma of the maxilla)

- Pathologic fracture
- Extraoral fistula
- Oral antral/oral-nasal communication
- Osteolysis extending to the lower border of the mandible or sinus floor[48]

HOW TO REDUCE THE RISK OF MRONJ OCCURRENCE?

The dentist should learn the patient's medication, duration of use, frequency, and dose and be in contact with the medical oncologist with a detailed anamnesis. The dentist should be able to identify the patient who is at risk. Since MRONJ, which develops as a side effect in patients using anti-resorptives, is specific to the jaws, many procedures have been listed to potentially reduce the risk of MRONJ.[50] At the very beginning of a preventive approach to MRONJ, one should be aware that antiresorptive drugs alter the healing capacity of bone. Whether the major factor is tooth extraction or local infection, the dentist should be aware of the risk, be able to educate the patient about it, maintain oral hygiene, and conservative treatments have an important role in preventing dental caries and treating existing caries.[5-7,51] Despite being a side effect of anti-resorptives, MRONJ is a "disease" whose risk factors are treatable by the dentist just like any other disease by Marx et al.[52]

In a study conducted among patients who developed MRONJ, active periodontitis was found in 84% of patients, dental abscess in 13%, dental caries in 29%, and failed root canal treatment in 11%.[52] Failure of debridement, which is indispensable for surgical treatment in patients with MRONJ, complicates the treatment of osteonecrosis and negatively affects the patient's quality of life. Therefore, eliminating the risk factors that facilitate the occurrence of MRONJ constitutes an indispensable part of the treatment.

Before Starting Medication:

Since the likelihood of MRONJ occurring after invasive dental procedures is high, medical oncologists should refer all patients with MRONJ-related drug group indications to the dentist for evaluation and consultation.[2,3,8] The dental team should prioritize practices that can prevent future tooth extractions and periodontal disease elimination, and teeth with abscesses and teeth that cannot be restored should be extracted in advance to allow time for wound healing.[17,18,51,53] Since MRONJ may develop due to mechanical trauma of large or multi-lobed lingual torus and large palatal torus with thin mucosa, it is recommended to remove them before drug treatment.[49-50,52]

DURING MEDICATION THERAPY

If the patient cannot be kept waiting due to the stage of cancer and the medical oncologist has to start drug treatment urgently, if there is no time for the treatments that the dentist should administer, the patient should be referred to the dentist for evaluation while the patient is under drug treatment since MRONJ develops depending on the repeated dose amount, duration, and route of administration of drugs.[28] Although tooth extraction is not recommended, fluoride application, supragingival scaling, restorative procedures, and root canal treatment have been recommended.[52]

The Importance of Treating Carious Teeth

Dental caries is an important health problem affecting most children and adults in many industrialized countries.[37] In the Global Burden of Disease study, in which 291 medical conditions were evaluated, untreated dental caries, affecting 3.1 billion people, was ranked as the most common among these diseases.[38-39] Although the reasons for tooth extraction include dental caries, periodontal problems, endodontic reasons, eruption failures, orthodontic treatment, and as part of prosthetic planning, the main reason is dental caries.[9-16] It has been reported that preventing the emergence of pathology in the hard tissues of the teeth with a preventive and therapeutic strategy, treating it when it occurs, providing adequate oral hygiene, and motivating the patient for its continuity will reduce the risk of MRONJ by reducing the need for oral surgery.[17,18]

In cancer patients, it has been suggested that there is a significant relationship between the condition of the oral cavity and the development of MRONJ. In MRONJ, high carious teeth, missing teeth, and filled teeth index (DMFTI) values have been associated with advanced stages of jawbone complications.[53] Advanced dental caries or periodontal disease requires invasive procedures that predispose to MRONJ.

According to a study by Kos, bisphosphonate users with MRONJ had poorer oral hygiene, more caries complications, and worse periodontal status compared to those without MRONJ.[57]

Eliminating the Effect of Reduced Saliva Flow (Hyposalivation)

Not only local drugs but also many systemic drug groups affect the condition of the oral cavity, salivary composition, and properties. In the literature, decreased salivation has been reported in patients using antiresorptive drug.[58] Saliva is not only an aid in digesting food, but also an important part of the oral cavity's innate immune system and wound healing. However, reduced salivary flow may weaken the oral cavity defense system by decreasing the number of antimicrobial peptides. Poor salivary flow can lead to reduced removal of fermentable carbohydrates from the oral cavity, making teeth more susceptible to decay. As tooth decay progresses, it can lead to infection of the jawbone. In addition, dry mouth leads to reduced bacterial clearance from oral tissues. Prolonged low oral pH levels and decreased buffer capacity can also lead to a harmful imbalance of oral microbes and disrupt the oral microbial flora.[59]

Importance of Oral Hygiene

It has been emphasized in many studies that Actinomyces species (species [spp.]) are colonizers that play an important role in oral biofilm formation, play an important role in the course of MRONJ, and are frequently detected in MRONJ lesions. When Actinomyces spp. crosses the mucosal barrier and passes into the submucosal region, only its pathogenic properties emerge, and at the same time, it can reach the anaerobic environment necessary to maintain its activity. In addition, the high distribution of Streptococcus spp. in MRONJ lesions has been frequently reported in recent studies.[60] For acute and chronic wounds, beta-hemolytic Streptococcus spp., Pseudomonas aeruginosa, and Staphylococcus aureus have been recognized as the main causes of delayed wound healing.[61] In patients with osteonecrosis, necrotic bone is painless because there is no innervation, but secondary infection and pain occur as a result of the activities of microorganisms.

Should Medication be Discontinued When MRONJ Occurs?

Drugs causing MRONJ accumulate in the bone matrix depending on the repeated dose amount, duration, and route of administration. Since bisphosphonates are resistant to hydrolytic degradation, their half-life in the bone matrix has been found to be longer than 11 years.[28] When osteonecrosis develops, it has been reported that necrosis does not regress with discontinuation of drug treatment.[5] The dentist should not intervene in the decision to terminate drug treatment, dose amount, duration, and route of administration.

CONCLUSION

MRONJ is a rare but potentially serious condition. The dentist has an important role in preventing osteonecrosis from occurring. Since treating drug-induced osteonecrosis of the jaw is hard and complicated, the dentist should be able to keep MRONJ from happening by lowering risk factors or, if that's not possible, at least make it happen later. Since most cases of MRONJ reported in the literature are associated with tooth extraction and oral surgical procedures, patient education, oral hygiene, and conservative treatment should minimize the need for invasive procedures.

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